

REMARKS

1. Preliminary Remarks

Claims 29, 30, 32, 35, 36, 38, 41, 42, 44, 62, and 63 are pending in this application. Claims 35 and 41 have been amended to correct a typographical error from the previous claim set. Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the application. Upon entry of the amendments and the remarks, claims 29, 30, 32, 35, 36, 38, 41, 42, 44, 62, and 63 will be pending and under active consideration.

2. Patentability Remarks

(a) 35 U.S.C. § 103(a)

On page 2 of the Office Action, the Examiner rejected claims 29, 30, 32, 35, 36, 38, 41, 42, 62, and 63 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent 5,260,305 (Dennick) in view of either U.S. Patent 5,126,145 (Evenstad) and Saito et al. (Arteriosclerosis and Thrombosis, 1991), or the combination of Evenstad, Saito, and U.S. Patent 5,116,610 (Broaddus). Specifically, the Examiner asserts that Dennick teaches niacin in an amount ranging from 75 mg to 2000 mg in a single or divided dosage forms. The Examiner further asserts that Dennick teaches the incorporation of swellable polymers such as gelatin and starch. In addition, the Examiner states that Dennick does not teach the combination of niacin and a swellable polymer such as hydroxypropyl methylcellulose, but that this element is taught by Evenstad. The Examiner declares that Evenstad teaches sustained or controlled release niacin tablets in combination with 5-30 wt. % hydroxypropyl methylcellulose, 2-5 wt % binders, 2-20 wt % hydrophobic component, lubricants, dyes, fillers, and extenders. The Examiner also asserts that Evenstad discloses niacin tablets with a dissolution profile of 10-35% release in 2 hours after oral ingestion, 40-70% in 8 hours, and at least 90% in 24 hours. Furthermore, the Examiner asserts that Broaddus discloses the administration of cholestyramine and polyol polyesters in the evening before meals or at bedtime. The Examiner also contends that Saito discloses the administration of simvastatin in the evening for cholesterol treatment, and that Saito discloses that a circadian variation exists, whereby the biosynthesis of cholesterol is accelerated at night. The Examiner stated that the combination of Broaddus and Saito would provide motivation to administer the niacin formulation in the evening. Applicant respectfully requests that the § 103(a) rejection be withdrawn, as the references cited by the Examiner fail to recite each and every element of the claimed invention, and provide no motivation to combine the disclosed elements.

Obviousness under 35 U.S.C. § 103(a) can only be established where the combined references teach or suggest each and every limitation of the claimed invention. *In re Royka*, 490 F.2d 981 (CCPA 1974). Additionally, there must exist some teaching, suggestion, or motivation to combine the various references. *See In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). The present claims are drawn, in their broadest iteration, to a method of achieving a balanced lipid alteration in a patient, whereby the method comprises orally administering to a patient once per day during the evening or at night at least two intermediate release formulations of nicotinic acid and a swelling agent to obtain a dose of at least 1500 mg nicotinic acid. Furthermore, the claimed invention requires that the at least two intermediate release nicotinic acid formulations have an *in vitro* dissolution profile whereby less than about 15% of the nicotinic acid is release after 1 hour, between 15% and about 30% is released after about 3 hours, between 30% and about 45% is released after about 6 hours, between 40% and about 60% is released after about 9 hours, between 50% and about 75% is released after about 12 hours, and at least about 75% is released after about 20 hours. The combination of Dennick in view of Evenstad and Saito, as well as the combination of Dennick in view of Evenstad, Saito, and Broaddus, alone or in combination do not disclose each and every element of the claimed invention, and one skilled in the art would have no motivation to combine the teachings of the various references.

As an initial matter, Applicant's response dated September 17, 2009, analyzed many of the references cited in the current Office Action, and is incorporated, in its entirety, herein. As stated in the specification of the current application, the novelty of the claimed method arises from a method that provides once a day administration of an intermediate release nicotinic acid formulation, in the evening, with minimal hepatotoxicity. None of the four references cited by the Examiner would suggest to a skilled artisan that nicotinic acid could be administered once daily, while still avoiding the hepatotoxicity associated with once daily treatment. Dennick discloses a combination treatment of pravastatin and nicotinic acid, "which may be administered in the dosage forms as described above [tablets or capsules] in single or divided doses of one to four times daily." (*See* Dennick, Col. 3, lines 64-66) Although, the specification states that the combination may be administered once daily, a skilled artisan would interpret Dennick as directed to a combination regimen whereby the pravastatin is administered once daily and the nicotinic acid is administered twice a day. *See* Dennick at column 6, lines 35-40 ("[patients] were randomized to 8 weeks of treatment of [double-blind placebo], [pravastatin sodium 40 mg] at bedtime, **NA [nicotinic acid] 1 g [twice a day] (as extended release capsules)** . . .") (emphasis added).

Furthermore, even if a skilled artisan were to view Dennick as disclosing once daily nicotinic acid administration, the skilled artisan would have no motivation to administer a sustained (i.e., extended or intermediate) release formulation once daily, due to the adverse affects associated with the use of

extended release nicotinic acid formulations. At the time of the filing for the claimed invention, it was well recognized within the art that sustained release nicotinic acid formulations were associated with higher incidences of hepatotoxicity and that sustained release nicotinic acid formulations “should be restricted from use.” *See* J.M. McKenney, JAMA, 1994; 271(9): 762-7. A similar conclusion was reached in an article authored by representatives of the Food and Drug Administration, warning of the hepatotoxicity associated with sustained release nicotinic acid formulations. *See* Radar, et al.: Hepatic Toxicity of Unmodified and Time-Release Preparations of Niacin, JAMA, 1992; 92: 77. These articles are also referenced in the specification, at pages 3-4. Applicant notes that similar arguments were raised in the previous Response, dated September 17, 2009, to which the Examiner responded in the current Office Action that “Applicant’s arguments . . . under 35 USC 103(a) [were] considered and are persuasive.” (Page 2 of the current Office Action).

Accordingly, in view of the Dennick reference, and the knowledge of a skilled artisan at the time the claimed invention was filed, it cannot be said that Dennick teaches or suggests the administration of an nicotinic acid formulation once a day. Even if we were to assume, for argument’s sake, that a skilled artisan could view Dennick as teaching or suggesting once daily nicotinic acid administration, the skilled artisan would not have any teaching, suggestion, or motivation to administer an extended (i.e., intermediate) release nicotinic acid formulation once a day due to the teachings of the art at the time, which suggested that sustained release formulations were associated with an increased risk of hepatotoxicity. Due to the fact that decreasing hepatotoxicity associated nicotinic acid treatment is one of the primary goals of the claimed invention, the knowledge in the art would teach away from the claimed invention.

Although the Examiner included an additional reference (Evenstad), the teachings and suggestions of Evenstad do not provide any grounds to cure the shortcomings of the previous prior art reference (Dennick). Specifically, as discussed previously, Dennick fails to teach or suggest the administration of an nicotinic acid formulation once a day and provides no motivation to administer an extended (i.e., intermediate) release nicotinic acid formulation once a day. Similarly, Evenstad does not teach a once daily nicotinic acid administration or formulation, and provides no motivation for one skilled in the art to pursue the claimed method. Evenstad describes the composition of the invention as a “sustained release tablet,” however, the specification makes it clear that the Evenstad composition is designed for dosing twice a day. The specification states “[t]ablets can be scored to permit [e]asy breakage into smaller doses for titration up to the standard 750 mg dose given twice daily.” (Col. 5, lines 58-60). The Evenstad reference makes no other references to the frequency of administration for the nicotinic acid composition. As such, Evenstad can only be said to disclose or suggest a composition

administered twice daily. Thus, due to the fact that neither Saito nor Broaddus disclose nicotinic acid treatments, it is clear that one skilled in the art would have no teaching, suggestion, or motivation, either implicitly or explicitly, to develop a method of administering nicotinic acid once a day, as a skilled artisan would likely believe that the once daily administration of an extended release nicotinic acid composition is not safe for the patient, given the reports of hepatotoxicity.

As a secondary matter, the prior art references do not teach or suggest that administering nicotinic acid in the evening may be accomplished, while minimizing hepatotoxicity. By the Examiner's own assertion, Dennick does not disclose administration of nicotinic acid in the evening or at night (See Page 3 of the Office Action). In addition, Evenstad does provide any language stating that the nicotinic acid formulation should be administered in the evening. The Examiner relies on Broaddus and Saito for support that "both references suggest administering at evening or bed time is safe and effective" (See Page 4 of the Office Action) Applicant respectfully argues that this assertion is incorrect. As the Examiner acknowledges in point 7 of the Office Action, Broaddus is directed to oral compositions comprising cholestyramine and polyol polyesters. As noted in point 8, Saito is directed to the administration of simvastatin. These two references are not only directed to drugs entirely different from nicotinic acid, they are also directed to drugs that belong to entirely different therapeutic classes of medications. Cholestyramine is a bile acid sequestrant that generally functions by binding bile acid, which in turn lowers cholesterol. Simvastatin is an HMG-CoA reductase inhibitor, and generally functions by inhibiting HMG-CoA Reductase, an enzyme responsible for producing cholesterol. In contrast, nicotinic acid generally functions by blocking the break down of fats, which, consequently reduces cholesterol secretion from the liver. Therefore, the mechanism of action for the three drug compounds is drastically different from one another. Furthermore, the side effect profile for each drug compound is also drastically different, with each agent associated with different side effects and different frequencies for side effects. Due to the fact that the three drug compounds effect the body in different ways, one skilled in the art would understand that simply because two of the three drugs have been shown to be safe and effective when administered at night (i.e., cholestyramine and simvastatin), it does not provide any evidence or suggestion that the third unrelated drug compound will also be safe and effective if administered at night.

In addition, the Examiner stated that "due [to] circadian rhythms[,] the cholesterol biosynthesis is more at night and therefore administering when at the time when the cholesterol synthesis is high is effective in reducing cholesterol levels" (See Page 4 of the Office Action) As such, it appears that the Examiner has also relied on Saito for support that administering a cholesterol-lowering medication at the time when cholesterol synthesis is at its highest would be obvious to one skilled in the art. Therefore,

the Examiner asserts that Saito suggests that circadian rhythms result in the highest cholesterol production at night, and, as a result, it would be obvious to administer the nicotinic acid formulations of the current invention at night. However, this assertion is incorrect, due to the fact that the Examiner has not taken into consideration the release profile of the claimed nicotinic acid formulation. Saito disclosed the administration of pravastatin tablets in the evening, and the pravastatin tablets were not extended release formulations. The findings in Saito do not take into consideration the adjustment to the administration time that would be needed due to the fact that an extended-release drug would not release the active compound as quickly as a non-extended release compound, and, consequently, would not reach therapeutic levels as quickly as the non-extended release formulation. Specifically, the claimed invention comprises a method of administering an intermediate release nicotinic acid formulation, whereby only about 15% to about 30% of the nicotinic acid is release after three hours, only about 30% to about 45% of the nicotinic acid is released after about 6 hours, only about 40% to about 60% of the nicotinic acid is release after about 9 hours, and only about 50% to about 75% of the nicotinic acid is released after about 12 hours. Unlike the immediate release pravastatin formulation tested in Saito, where 100% of the active drug compound is released immediately, the nicotinic acid formulation gradually releases active compound over a prolonged period of time, taking about 12 hours to release 75% of the active ingredient. Therefore, one skilled in the art would understand that the teachings of Saito are not applicable to drug compounds with an extended (intermediate) release profile, because the artisan would need to consider the pharmacokinetic qualities of the active compound and the release profile to determine the optimal time of administration, considerations that were not present in the Saito experiment.

Thus, Saito and Broaddus do not teach or suggest the administration of nicotinic acid in the evening because both references are directed to the administration of different drug compounds, with distinct mechanisms of action and pharmacodynamic profiles. Accordingly, the findings that cholestyramine and simvastatin are safe and effective when administered at night, as disclosed in Broaddus and Saito, respectively, does not teach or suggest that the administration of nicotinic acid at night is also safe and effective. Furthermore, the Examiner's reliance on Saito's disclosure that pravastatin is optimally administered at night due to circadian rhythms (and their effect on cholesterol synthesis) does not suggest to a skilled artisan that nicotinic acid is also optimally administered at night, because of the difference in release profiles between the two dosage forms (i.e., immediate release vs. extended release). Consequently, neither Broaddus nor Saito teach or suggest that an intermediate release nicotinic acid formulation should be administered once a day in the evening, an element that is a requirement of the claimed invention.

As stated previously, a finding of obviousness under 35 U.S.C. § 103(a) is only proper if each and every element of the claimed invention is taught or suggested by the prior art, with a motivation to combine the various elements. The references cited by the Examiner do not teach or suggest a once daily administration of an intermediate release nicotinic acid formulation and do not teach or suggest the administration of nicotinic acid in the evening. Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) be withdrawn.

3. Conclusion

Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

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